Implementing Metrological Traceability in Laboratory Medicine – A Manufacturing Perspective

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Agenda

- What is metrological traceability
- What must a manufacturer do to comply with ISO 17511 and 18153
- What resources are available to the manufacturer to meet these requirements
- Where are the difficulties
- How can the NCCLS continue to help

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What is Traceability

Metrological traceability – Property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparisons all having stated uncertainties

ISO 17511, VIM:1993,6.10

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Why Traceability

"For measurements of quantities in laboratory medicine, it is essential that the quantity is adequately defined and the results reported to the physicians … are adequately accurate (true and precise) to allow correct medical interpretation and comparability over time and space."

ISO 17511- Introduction

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Traceability is Nothing New

- A National Understanding for the Development of Reference Materials and Methods for Clinical Chemistry
  – J. Boutwell, Editor (1978)
- NCCLS National Reference Council – NRSCL Reference systems
- NIST Activities
- IFCC Reference procedures and materials
- Cholesterol Reference Method, IFCC HbA1c and NGSP networks

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Metrological Traceability Standards

- ISO/TC 212 – Clinical Laboratory Testing and in vitro diagnostic test systems
  - Secretariat – NCCLS
- European Committee for Standardization (CEN)
- Cooperative preparation of 5 Standards describing elements of Metrological Traceability

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The Standards

- ISO 17511 Traceability of values assigned to Calibrators
- ISO 18153 Traceability of values assigned to to calibrators (enzymes)
- ISO 15193 Presentation of reference measurement procedures
- IOS 15194 Description of reference materials
- ISO 15195 Requirements for Reference measurement laboratories

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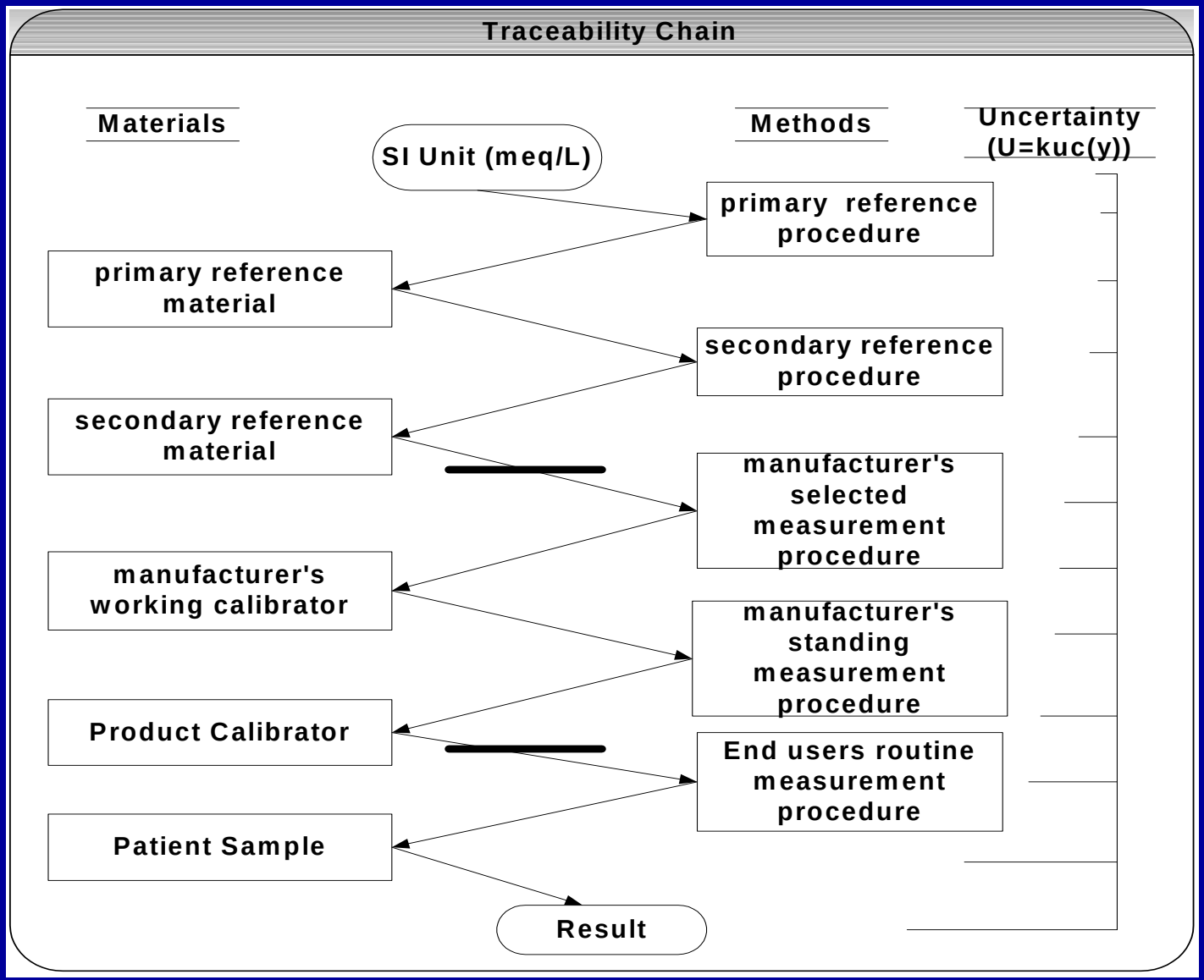
Traceability Chain



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Manufacturer's Obligations

- IVD Directive –
  - The traceability of values assigned to calibrators and/or control materials must be assured through reference measurement procedures and/or available reference materials of a higher order
  - Manufacturer must provide to users information about the traceability of the calibrators used with the device
  - Manufacturer is not obligated to use the ISO/CEN standards mentioned before but must have a system that is equal to or better than the standards

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Manufacturer's Obligations

- Design a traceable calibrator
- Validate the calibrator
- Document the traceability of the calibrator
- Provide the information to customers upon request

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Manufacturer's Obligations – Define the Measurand

- What is being measured
  - Units
  - Sample
  - Properties

- hCG – Whole Molecule? Subunits? IU? Mass? Mixtures? activity? Different types of samples?

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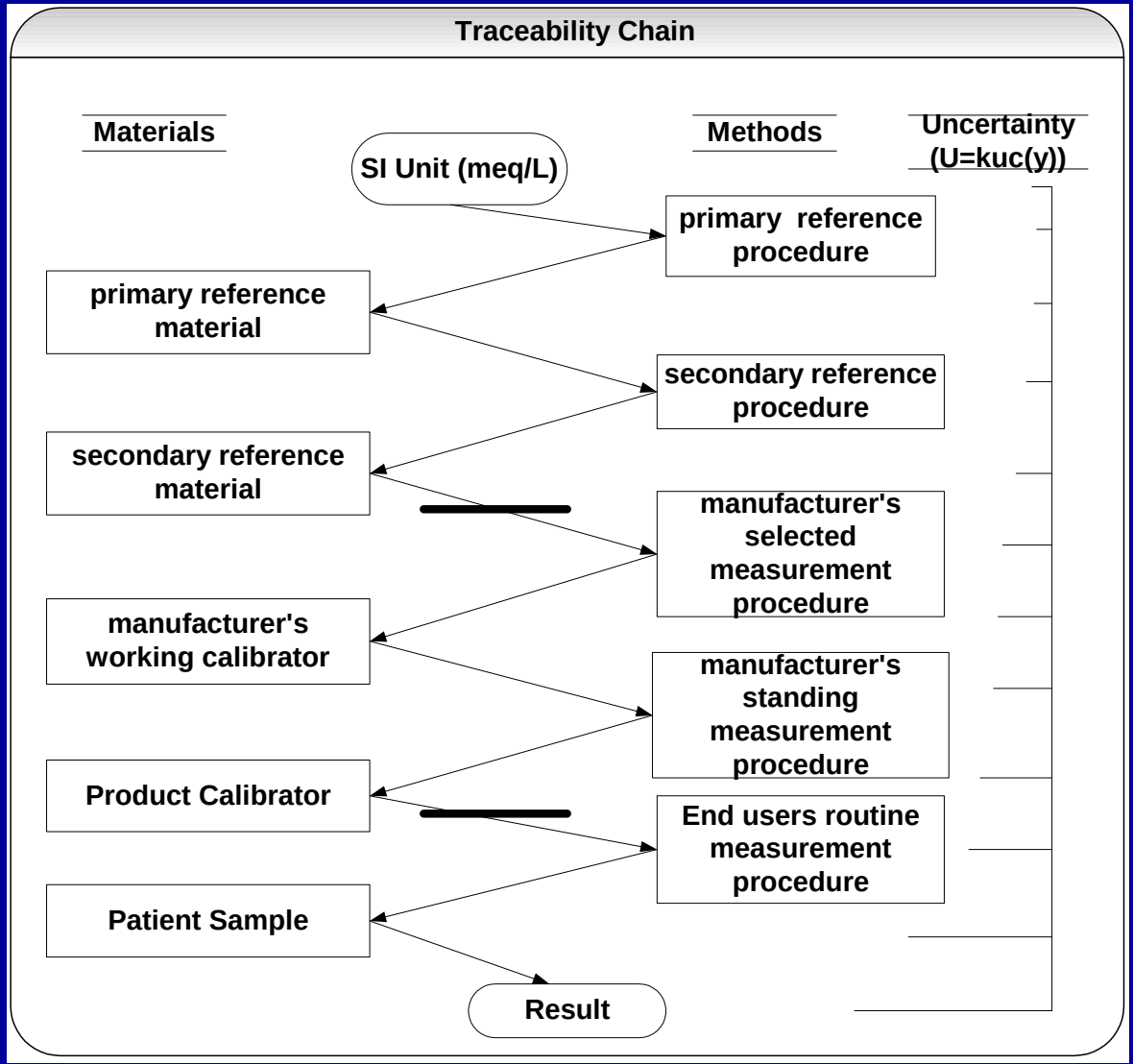
Manufacturer's Obligations – Define & Document the comparisons



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Manufacturer's Obligations – Validate the calibrator including the comparisons

- Demonstrate that the entire value assignment process works
- Document the transfer processes
- Determine the uncertainty of the transfer processes
- Demonstrate the commutability of the transfer processes, when a reference procedure exists
- Responsible for the processes "between the lines" (or within their control)

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Manufacturer's Obligations

Uncertainty

- Uncertainty (of measurement)
  - Characterizes the dispersion of values that could be reasonable be attributed to the measurand
  - Principles given in the "Guide for the expression of uncertainty in Measurement" GUM:1993)
  - Numerical (assigned) value +/- Uncertainty k=2 is the standard
  - Uncertainty is cumulative

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Uncertainty Resources

- "Guide for the expression of uncertainty in Measurement" GUM:1993)
- Quantifying Uncertainty in Analytical Measurement (EURACHEM/CITAC Guide (second edition)
  - http://www.eurachem.ul.pt/guides/QUAM2000-1.pdf
- Evaluation of measurement uncertainty in clinical Chemistry
  - http://www.irmm.jrc.be/imep/imep17/ge_r_im_34_01.pdf

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Manufacturer's Obligations – Validation - Commutability of the Product Calibrator

- Must demonstrate the relationship between the measurement results by the routine procedure and the reference procedure is the same for all relevant human samples
  - The objective is to obtain results from the medical device that are "as close as required" to that obtained if the reference measurement procedure is used
  - Must have a reference measurement procedure qualified for all relevant samples
  - Must measure the same quantity as the reference procedure
  - Must have a definition of "as close as required"

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Commutability - Resources

EP9-A Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline

- Consider reduced number of samples
- Protocol is performed on more than one instrument each calibrated more than one times

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Manufacturers Obligations – Validation - Commutability of the Working Calibrator

- "If the mathematical relationship between the results of the reference measurement procedure and the routine measurement procedure for human samples is not significantly different form that found for the manufacturers working calibrator(s), then commutability shall have been demonstrated"

– ISO 17511, 7.2

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Commutability - Resources

EP14-A Evaluation of Matrix Effects; Approved Guideline:

- Assure the range of samples is representative
- Strongly recommend only native samples compared with working calibrators
- Utilize replicate results and multiple calibrations of the commercial method

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Example - Commutability

- Creatinine method
- Existing value assignment method will no longer be available
- New value assignment process recommended
- Existing value assignment process yielded patient results with a slope within 1.5 %of the reference method.
- Preliminary data indicated a slight increase in assigned values with the new method
- Commutability Studies conducted.

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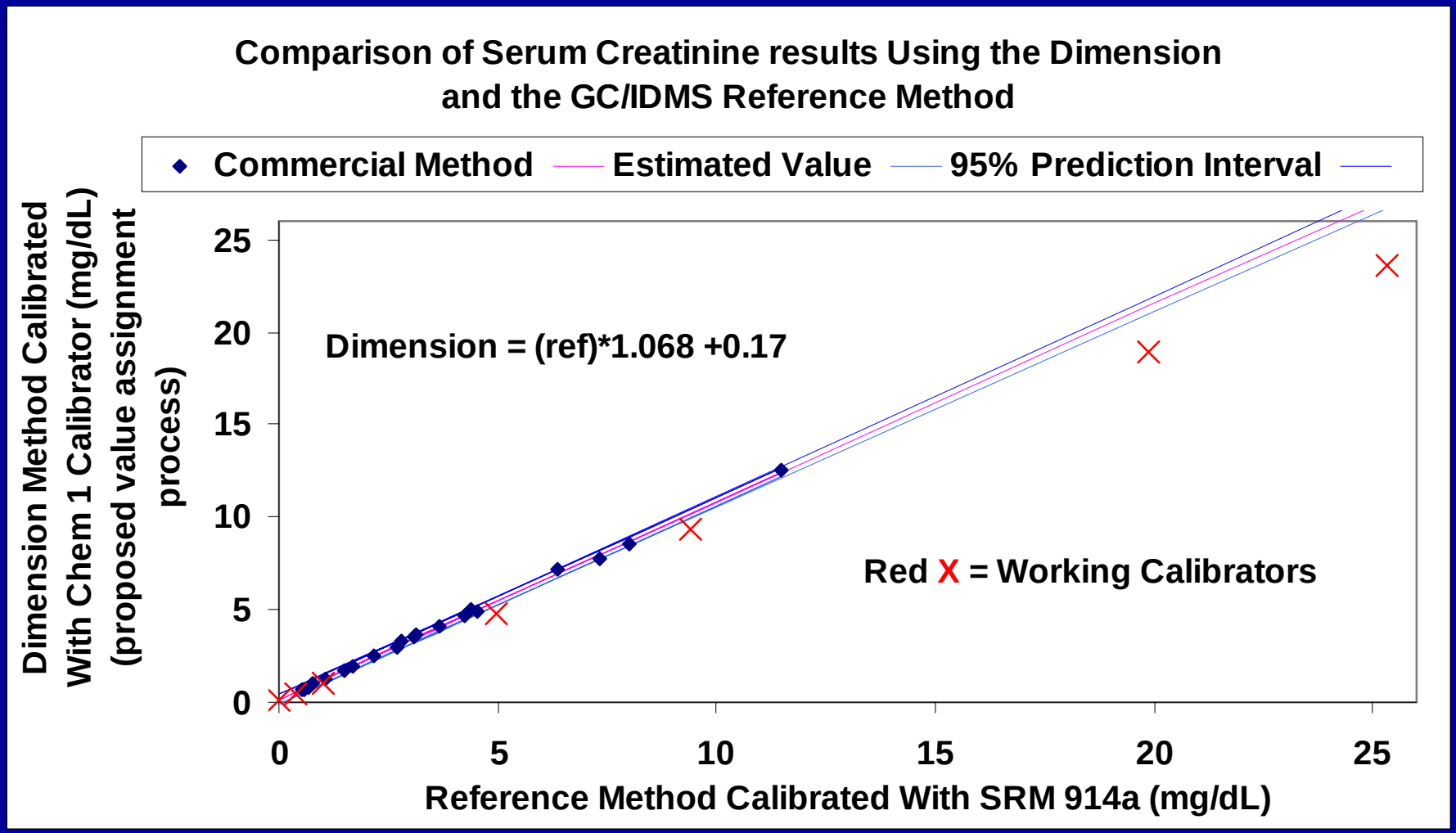
Example - Commutability



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Example - Commutability

End Result:

- The proposed method was not implemented
- Working calibrators that are commutable are being developed

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Resources Available to the Manufacturer

- NCCLS Documents
  - EP9
  - EP14
  - Reference systems
- EUROCHEM/CITAC Documents
  - Traceability
  - Uncertainty

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Resources Available to the Manufacturer

- ISO Documents
  - ISO 17511, ISO 18153 (Describing traceability)
  - ISO 15193, ISO 15194 and ISO 15195 (Describing requirements for reference measurement procedures, reference materials and Reference measurement laboratories
  - Guide to the expression of uncetainty

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Resources Available to the Manufacturer

- Joint Committee for Traceability in Laboratory Medicine
  - Joint Committee supported by IFCC, BIPM and ILAC
  - Objective to provide lists of reference materials, reference procedures and reference measurement laboratories which meet ISO requirements

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Opportunities

- Of the over 400 types of quantities measured in the clinical laboratory, the JCTLM is listing:
  - 44 Reference measurement procedures
  - 95 Reference Materials
  - Laboratory Lists are still under development

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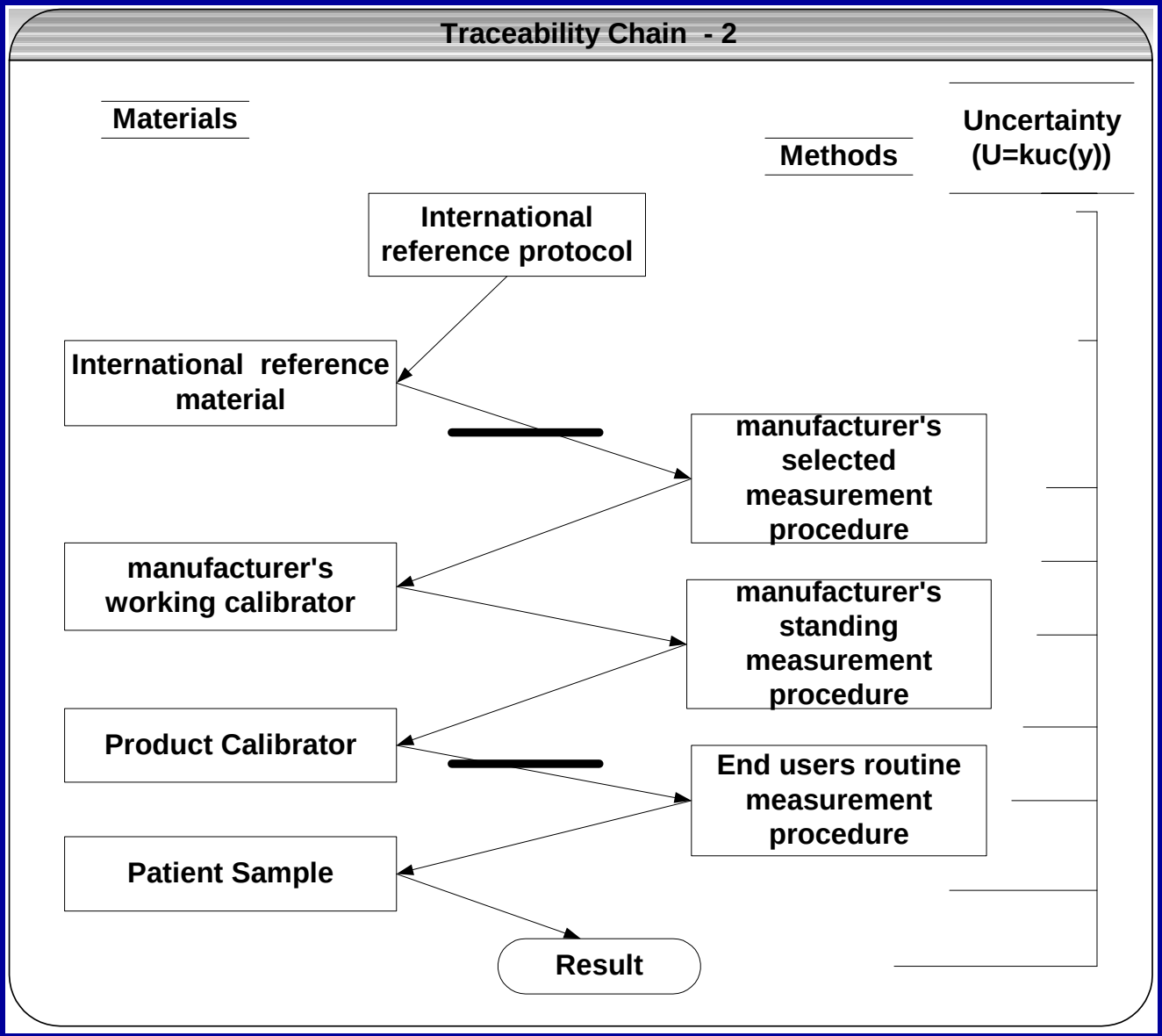
Missing Materials or Procedures



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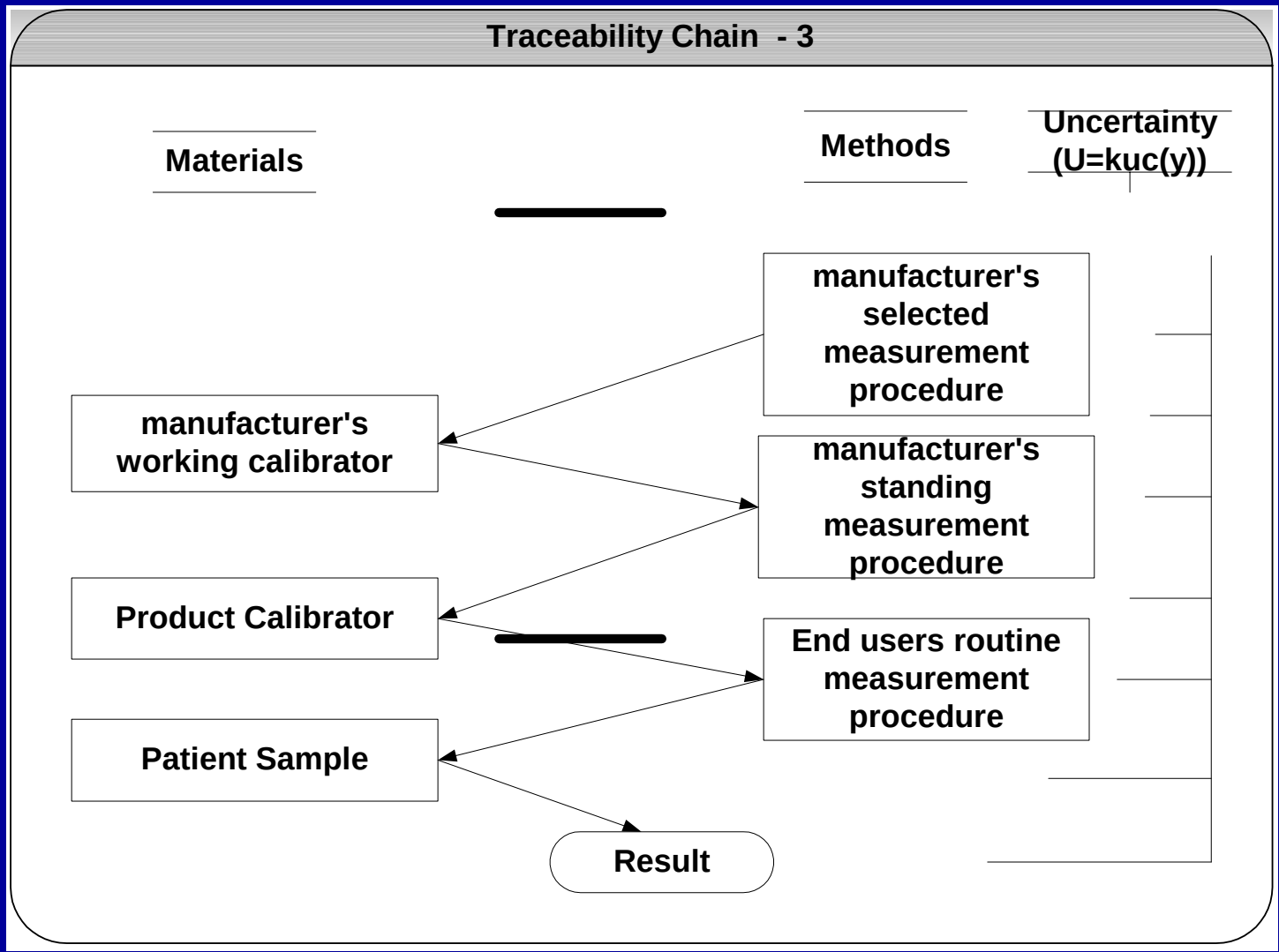
Missing Materials and Procedures



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Opportunities

- With the exception of the 5 documents developed by ISO TC 212, none of the other procedures or documents are specifically designed for use by manufacturers of IVD Calibrators.
  - Technical Limitations
  - Not specific for this application

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Opportunities

- Traceability information, including uncertainty is required for certification of service laboratories by several countries.
  - A manufacturer who does not provide the information in this format will find himself at a disadvantage.
  - Application of the requirements must be uniform to minimize “over claiming” the uncertainty of a method or calibrator

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Opportunities

- Impact to the end user
  - When references and approaches change, the patient results will change.
  - Manufacturer needs to minimize customer confusion
    - **Impact on expected values**
    - **Impact on QC results**
    - **Shifts when calibrators are changed**
  - Customers needs to understand what they are getting

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How Can The NCCLS Help?

- Additional Guidelines
  - Traceability (In Progress)
  - Uncertainty
  - Commutability
  - What to do with the information

  These need to be both IVD Manufacturer and clinical laboratory focused

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Conclusion

- Traceability, according to the ISO documents, has the potential to further harmonize laboratory results.
- It reinforces the need for a scientific basis for value assignment processes
- But - Continued support is necessary to maintain the system – Therefore:

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We are not done, yet

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THANK YOU FOR YOUR ATTENTION

Rick

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